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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/892,591	06/27/2001	Tillman U. Gerngross	GFI 100	2292

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EXAMINER	
QIAN, CELINE X	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 03/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/892,591	GERNGROSS, TILLMAN U.	
	Examiner	Art Unit	
	Celine X Qian	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 January 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35-64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 June 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/14/02, 8/23/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 35-64 are pending in the application.

Election/Restrictions

Applicant's election without traverse of Group I (claims 1-23) in Paper No. 14 is acknowledged. Applicants cancelled claims 1-34. Newly added claims 35-64 are directed to the elected subject matter of Group I. Accordingly, claims 35-64 are currently under examination.

Information Disclosure Statement

The information disclosure statement submitted on 8/23/02 is a duplication of the information disclosure statement submitted on 7/5/02. Therefore, only one initialed copy of 1449 will be mailed with this office action.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (for example, see page 18 and 39). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 35-64 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described

in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The written description requirement is set forth by 35 U.S.C. 112, first paragraph which states that the: "*specification* shall contain a written description of the invention. . .[emphasis added]." The written description requirement has been well established and characterized in the case law. A specification must convey to one of skill in the art that "as of the filing date sought, [the inventor] was in possession of the invention." See *Vas Cath v. Mahurkar* 935 F.2d 1555, 1560 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). Applicant may show that he is in "possession" of the invention claimed by describing the invention with all of its claimed limitations "by such descriptive means as words, structures, figures, diagrams, formulas, etc., that fully set forth the claimed invention." See *Lockwood v. American Airlines Inc.* 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

In analyzing whether the written description requirement is met, it is first determined whether a representative number of species have been described by their complete structure. Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. The claims recite "a lower eukaryotic host cell that does not display a 1, 6-mannosyltransferase activity." The claimed genus of the host cell potentially encompasses a large number of cells from different species, such as yeast, fungus, insect or plant, that lack 1, 6-mannosyltransferase activity. The specification only discloses two OCH1 mutant strains of *Saccharomyces cerevisiae* and *Pichia pastries* that lack 1, 6-mannosyltransferase activity. The specification fails to teach whether OCH1 gene encodes 1, 6-mannosyltransferase in other types of yeast strain or cells from other species. The

specification thus only teaches the functional aspect of the claimed host cell but not the structural characteristics. As such, the structural functional relationship is missing.

The claims also recite "one or more enzymes for production of a Man5GlcNAc2 carbohydrate structure. The claimed genus encompasses a large number of enzymes that can convert a substrate of any kind to Man5GlcNAc2 structure. The specification only disclose a 1, 2-mannosidase from *Aspergillus saitoi* that is able to cleave high mannose glycoprotein to Man5GlcNAc2 carbohydrate structure. The specification fails to disclose other types of enzymes that are involved in the synthesis of Man5GlcNAc2, other kind of mannosidase that can produce Man5GlcNAc2 carbohydrate structure, or 1, 2-mannosidase from other species that can produce Man5GlcNAc2 carbohydrate structure. The specification thus fails to describe the claimed invention by their complete structure nor other identifying characteristics. Therefore, the written description requirement is not met.

Claims 35-64 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to

make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

The nature of the invention

The nature of the invention is a method of producing a human-like glycoprotein in a lower eukaryotic cell that does not display a 1, 6 mannosyltransferase activity with respect to the N-glycan on a glycoprotein, the method comprising the step of introducing into the host cell one or more enzymes for production of a Man5GlcNAc2 carbon structure, wherein at least 30% is produced within the host cell which can serve as a substrate for GnT1 *in vivo*.

The breadth of the claim

The breadth of the claim is very broad. The broadest claim is drawn to a method of producing a human like glycoprotein in any type of lower eukaryotic cell lacking 1, 6-mannosyltransferase activity by introducing any kind of enzyme involved in the synthesis of Man5GlcNAc2 into the host cell, and result in the production of Man5GlcNAc2 for over 30% of glycoprotein. The lower eukaryotic cell encompasses cell from different species such as yeast, fungus, algae or insect.

The teaching of the specification and working examples

The teaching of the specification is limited. The specification teaches that mutant host cells lacking 1, 6-mannosyltransferase activity can be generated by identifying the gene encoding said protein and introducing mutation to said gene. The specification teaches that library of genes encoding enzymes involved in the generation of human like glycoprotein such as mannosidases, GnTs, and UDP-Gal transporter can be introduced into the host cell and thus generated proteins with glycosylation pattern similar to those seen in mammalian cells.

However, the specification fails to teach whether such method can produce Man5GlcNAc2 carbon structure, a intermediate for the production of human-like protein, over 30% of the total glycoprotein produced. Nor does the specification provide any working examples for the claimed method. Therefore, one skilled in the art would have to rely on the teaching of the prior art to practice the claimed method.

The state of art at the time of filing and the level of predictability in the art

At the time of filing, there is no known system in lower eukaryotic cells that produces glycoprotein which has Man5GlcNAc2 carbon structure over 30% of the total glycoprotein produced. The prior art teaches that the yeast share the early steps of the mammalian Asn-linked glycosylation pathway. However, the mature Asn-linked oligosaccharides of yeast are mannan glycans and are highly antigenic against mammals. Yeast expresses mannoysltransferase that produces glycoproteins with high mannose structure, whereas mammalian cells expresses specific mannosidases to trim the mannan chain, GnTs to transfer GlcNAc structure, and specific transferase to add galactose, glucose or sialic acid to terminal carbon structure. Chiba et al. (1998) report the first time that in a yeast system, a glycoprotein with Man5GlcNAc2 carbon structure is produced by introducing a 1, 2-mannosidase into a yeast host strain that lack mannosyltransferase activity. However, Chiba et al. report that the Man5GlcNAc2 carbon structure is 27% among all the glycoprotein produced. Chiba et al. also indicate that the localization of the mannosidase is important because the trimming of sugar chains in yeast does not occur when the enzyme is mislocalized (see page 26302, 2nd col., 1st paragraph). On the other hand, localization signal from one organism does not necessarily function in another organism (see specification page 4, last paragraph, and Krezdorn et al., 1994). As such, it is

unpredictable whether the method taught by Chiba et al. can be reproduced in another system. In addition, whether the method would result in production of more than 30% Man5GlcNAc2 carbon structure is unpredictable.

The state of art at the time of filing does not identify all the enzymes responsible for Man5GlcNAc2 production. The prior art does not teach enzymes that would prevent Man5GlcNAc2 formation other than 1, 6-mannosyltransferase in the yeast. Without knowing the glycosylation process in a particular type of lower eukaryotic host cell, whether Man5GlcNAc2 can be produced or produced for more than 30% in said host cell by simply introducing one or more enzyme such as a mannosidase is unpredictable. The specification fails to teach a method of making humanized glycoprotein in a lower eukaryotic cell in which the Man5GlcNAc2 is more than 30%. The specification also fails to teach any steps that would modify the method taught by Chiba et al. and increase the production of Man5GlcNAc2. Without the teaching from the specification, one of skilled in the art would have to engage in undue experimentation to practice the method as claimed. Therefore, the claimed method is not enabled by the specification.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 35-64 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 35-64, the term "human-like glycoprotein" renders the claims indefinite because the specification does not clearly set forth the definition of this term. It is unclear how to determine this glycoprotein is "human-like." For example, is the mere presence of Man5GlcNAc2, a precursor for further glycosylation in human cells, enough to define the glycoprotein is "human like?" Or, which one of the glycoprotein depicted in the Figure 1B is considered to be human like?" Without a clear definition, the metes and bounds of the claim cannot be established.

The recitation of "at least 30% Man5GlcNAc2 is produced" also renders the claims indefinite because it is unclear what this percentage refers to. For example, is this percentage relative to total protein produced within the host cell, total sugar synthesized within the cell, total DNA produced within the host cell, or all of the above?

Regarding claims 37 and 61, the recitation of "representative enzymes in the organelle" renders the claims indefinite because it is unclear what criteria the enzymes must have to be considered as a representative enzyme in an organelle. As such, the metes and bounds of the claims cannot be established.

Regarding claim 45, the term "NeuNAc-Gal-GlcNAc-Man" renders the claim indefinite because the specification does not teach such molecule. Specifically, it is unclear what "Neu" stands for.

Regarding claims 58 and 61, the word "derived" renders the claims indefinite because the nature and number of derivative process is unclear. As such, the metes and bounds of the claim cannot be established.

Regarding claim 59, the recitation of "one enzyme" renders the claim indefinite because it is unclear which enzyme it is referring to. Claim 35 recites the introduction of one or more enzymes, whereas claim 54 recites the further introduction of a nucleic acid encoding one or more enzymes. It is unclear the enzyme recited in claim 59 refers to the former or the latter.

Claim 61 recites the limitation "catalytic domain" in line 1. There is insufficient antecedent basis for this limitation in the claim. Neither parent claim 35 nor 54 recite this limitation.

Claims 35-64 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: how to determine a human-like glycoprotein is produced.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 35-42, 46-48, 52, 54-56, 59 and 60 are rejected under 35 U.S.C. 102(b) as being anticipated by Chiba et al (IDS).

The claims are drawn to a method for producing a human-like glycoprotein in a lower eukaryotic host cell that does not display a 1, 6 mannosyltransferase activity with respect to N-glycan on a glycoprotein, the method comprising introducing into host cell one or more enzymes for production of a Man5GlcNAc2 carbohydrate structure (35, 54). The claims are further drawn to such methods wherein said enzymes have optimal pH at the target location (36, 37, 56),

wherein the enzyme is targeted by fusion of a target signal peptide to ER or Golgi to the enzyme (38, 39, 59, 60), wherein the enzyme is a mannosidase (40, 41, 55), wherein the glycoprotein has fewer than six mannose residues (42), wherein the host cell is a Saccharomyces cerevisiae (46), or wherein the host cell lack expression of mannosyltransferase (47, 48). Moreover, claim 52 is drawn to such a method that further comprises isolating the glycoprotein from the host.

Chiba et al. disclose a method for producing a human-like glycoprotein by introducing into yeast host cells (S. cerevisiae) a vector comprising nucleic acid encoding a α 1, 2-mannosidase linked to a ER signal peptide (HDEL) (see page 26300, 2nd col., last paragraph through page 26301, 1st col., 2nd paragraph). Chiba et al. further disclose that the host cell is a mutant yeast strain lacking mannosyltransferase expression (OCH1, MNN1 and MNN4) (see page 26299, 1st col., last line through 2nd col., 2nd line). Moreover, Chiba et al. disclose that the result yeast strain is able to produce the Man5GlcNAc2 carbon structure, and thus the mannosidase is functional at the pH at the target organelle (see Figure 6, page 26302, 1st col., 3rd paragraph). Lastly, Chiba et al. disclose that the glycoprotein produced in isolated from the host and further analyzed (page 26302, 1st col., 3rd paragraph). Therefore, Chiba et al. disclose the instant claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 571-272-0777. The examiner can normally be reached on 9:30-6:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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